PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Process for the Encapsulation of Acetylsalicylic Acid Particles

We, THE NATIONAL CASH REGISTER COMPANY of Dayton in the State of Ohio, and Baltimore in the State of Maryland, United States of America, a Company organized under the laws of the State of Maryland, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to a process for the encapsulation of powdered acetylsalicylic acid in ethyl cellulose and to capsules prepared by this process.

In United Kingdom Patent Specification No. 965,070 there is disclosed a process for the micro-encapsulation of tiny particles of acetylsalicylic acid, each particle entity being confined and protected in a wall of ethyl cellulose, which has been grown thereon in incremental deposits from an agitated hot liquid solution of the ethyl cellulose in cyclohexane. This process includes the step of liquid-liquid phase separation brought about by cooling of the ethyl cellulose solution. The phase separation is rendered possible by the presence of a phase separation inducing agent which takes no part in the composition of the capsule wall except as a small innocuous amount which may be carried thereinto by entrainment.

Acetylsalicylic acid, as manuactured, commonly contains some dissociation products. This dissociation content increases slowly when the acid is in contact with certain materials, especially at high humidity. Therefore, in the encapsulation of acetylsalicylic acid it is highly desirable to inhibit its hydrolysis as far as possible both during and after the encapsulation process. To achieve this end the aforementioned application recommends the addition of a small amount of acetic anhydride to the hot manufacturing system.

It has now been found that by pre-heating the acetylsalicylic acid with an acid buffering salt, the seriousness of the problem of hydrolysis as concerns the acetylsalicylic acid in the presence of moisture is even further diminished.

Thus, according to one aspect of the present invention, a process for the encapsulation of minute particles of acetylsalicylic acid in hydrophobic polymeric material, includes the steps of preparing a hot solution in cyclohexane of ethyl cellulose and a phase separation inducing agent; dispersing in said solution by agitation particles of powdered acetylsalicylic acid; cooling the dispersion under continued agitation to cause the ethyl cellulose so separate out from solution and form a liquid phase depositing on and around the acetylsalicylic acid particles which phase solidifies by disolvation as cooling progresses; recovering the so formed capsules from the solution and washing them in a solvent for the phase separation inducing agent; the particles of the acetylsalicylic acid being coated with an acid buffering salt prior to being added to the solution.

According to another aspect of the invention, there are provided minute capsultes each consisting of a seamless wall of ethyl cellulose retaining at least one particle of acetylsalicylic acid coated with a buffering salt selected from the mono-basic phosphates of sodium, potassium or ammonium.

It has been further found that the above-mentioned problems of hydrolysis can be still further alleviated by using polyethylene as the phase separation inducing agent.

In order that the invention may be better understood, a number of embodiments there-

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of will now be described, by way of example.

EXAMPLE I

To perform the pre-treatment of the acetylsalicylic acid particles, according to the invention, there are mixed together at room temperature the following materials:

Water (distilled or ionized)	80	lbs.
Mono-basic potassium phosphate	4.3	lbs.
Acetylsalicylic acid (powdered to pass a sieve with openings of 0.5 millimeter)	30	lbs.
Phosphoric acid sufficient to bring pH to 2.3		

This mixture is stirred for 10 minutes more or less, at room temperature (20 degrees to 25 degrees Centigrade), and the residual so-treated acetylsalicylic acid then is recovered suitably by filtering and drying. The so treated particles are then encapsulated. For this purpose the following dispersion is made at room temperature:

Cyclohexane	490	lbs.
Polyethylene (as specified below)	10	lbs.
Acetic anhydride	2.5	lbs.
Ethyl cellulose (as specified below)	3	lbs.

Ethyl cellulose has an ethoxyl content of 48.0—49.5 per cent, which gives the necessary solution properties in cyclohexane near its boiling point, such ethyl cellulose material not being soluble therein at room temperature, and has a viscosity of 90—105 as determined using a 5 per cent by weight solution in an 80/20 toluene/ethanol bath. The polyethylene selected is a low viscosity material having a molecular weight of approximately 7000, and a softening point of 100—101 degrees Centigrade.

Both the ethyl cellulose and the polyethylene are soluble in cyclohexane at 80 degrees Centigrade and the system is agitated and heated to that point before the introduction thereinto of 105 pounds of the treated acetylsalicyclic acid in the specified particular size. After complete dispersion has been reached, with continued dispersion being maintained by agitation, the temperature is dropped to room temperature over a period of approximately two hours, by artificial cooling if necessary, during which time the ethyl cellulose detaches itself from the homogeneous solution as a separate liquid phase which deposits on and wraps the individual acetylsalicylic acid particles in a liquid wall. As cooling progresses the deposited ethyl cellulose becomes more or less solid by desolvation, while the polyethylene for the most part has remained in the cyclohexane as extremely fine particles of solid material. The ethyl cellulose coated acetylsalicylic acid particles may then be recovered by filtering, and hardened by further drying of the cyclohexane therefrom. The filter-cake is washed several times in fresh cyclohexane, or other volatile solvent, to remove residual polyethylene and acetic anhydride which may have adhered to or have been entrained on the capsule walls. After washing is completed, the encapsulated material may be filtered dry to a cake and placed on a vibrating-screen-classifier, and dry air blown through the classifier screen at 40 degrees Centrigrade for a period of 15 minutes to half an hour, after which time the capsules are removed from the vibrating screen classifier and placed on trays in a 40 degrees Centigrade dry air circulating oven to remain until the residual cyclohexane, or other solvent, is removed to leave approximately 200 parts per million by weight. Other methods of recovering the capsules, as by centrifuging or decanting, may be used. This material is fit for medication as it is, or may be dispersed in a palatable non-solvent, or tableted with or without binder material.

Instead of the mentioned mono-basic potassium phosphate, other buffering salts, such as mono-basic sodium phosphate mono-hydrate or mono-basic ammonium phosphate may also be advantageously used for the pre-treatment of the acetylsalicyclic acid particles.

EXAMPLE II

In this example the amount of ethyl cellulose as used in Example I may be varied from the 3 lbs. noted for the particular mixture by an increase in amount thereof up to 15 lbs.

EXAMPLE III

In this example, which pertains to capsules with thicker walls, the process is similar to Example I but the amount of ethyl cellulose used is increased to 10 lbs. from 3 lbs., and the amount of acetylsalicylic acid is reduced from 105 lbs. to 90 lbs. It will be appreciated that this formulation differs from that of Examples I and II in that there is a change both in the ethyl cellulose content and in the acetylsalicyclic acid content, relative to the other ingredients, and will give an accordingly thicker coating on the acetylsalicyclic acid particles, with a solids content in the dispersion of 100 lbs. in terms of ethyl cellulose and acetylsalicylic acid, whereas the solids content of Example I is 108 lbs. and that of Examples II 120 lbs.

EXAMPLE IV

In this example the composition of Example I is used, except that a quantity of an acetylated monoglyceride of from one to three times that of the ethyl cellulose by weight is added, which lowers the phase-separation temperature of the ethyl cellulose to around 50 degrees Centigrade.

The specified particle size of the acetylsali-

cylic acid may be varied as desired to any dispersible size conformable to the parameters of the materials used in the composition as far as the coverage of the surface area by the particles of the ethyl cellulose is concerned.

The particulate conformation of the particles of acetylsalicylic acid may be of any shape controlled by the method of comminution, precipitation, or other means of formation.

The product made by this process is completely tasteless, and provides sustained release of the medicament in the human stomach and intestinal tract.

While it has been stated that there is a certain order of additioin of the components to the composition with respect to the time of raising the temperature and the cooling thereof, it is to be understood that the process is not dependent on the order of addition and all of the component materials thereof may be assembled in the cold state, as at room temperature, for subsequent use by the later-undertaken steps of heating and agitation to bring about the formation of the separated ethyl cellulose solution phase and the encapsulation of the dispersed particles of acetylsalicyclic acid with it to form embryonic capsules which later are stabilized by cooling the system.

The relative amounts of capsule forming materials dispersed in the cyclohexane can be varied greatly but the cyclohexane forms the major portion of the system provide a voluminous dispersion medium the insoluble acetylsalicylic acid. For instance, based on the weight of cyclohexane, 25 per cent or less of acetylsalicyclic acid, 1 to 3 per cent of the specified polyethylene, and ½ to 3 per cent of the specified ethyl cellulose may be used.

WHAT WE CLAIM IS:—

1. A process for the encapsulation of minute particles of acetylsalicylic acid in hydrophobic polymeric material, including the steps of preparing a hot solution in cyclohexane of ethyl cellulose and a phase separation inducing agent; dispersing in said solution by agitation particles of powdered acetylsalicylic acid; cooling the dispersion under continued agitation to cause the ethyl cellulose to separate out from solution and form a liquid phase depositing on and around the acetylsalicylic acid particles, which phase solidifies by disolvation as cooling progresses; recovering the so formed capsules from the solution and washing them in a solvent for the phase separation inducing agent; the particles of the acetylsalicylic acid being coated with an acid buffering salt prior to being added to the solution.

2. A process according to Claim 1, wherein as the phase separation inducing agent, polyethylene, having a molecular weight of approximately 7000 and a softening point of 100 to 101 degrees Centigrade, is used.

3. A process according to Claim 1, wherein the ethyl cellulose constitutes from ½ to 3 per cent, by weight, of the cyclohexane.

4. A process according to Claim 1, wherein the powdered acetylsalicylic acid constitutes 25 per cent or less, by weight, of the cyclohexane.

5. A process according to Claim 2, wherein the polyethylene constitute from 1 to 3 per cent, by weight, of the cyclohexane.

6. A process according to any one of the preceding claims, wherein a quantity of an acetylated monoglyceride of from 1 to 3 times that of the ethyl cellulose, by weight, is added to the dispersion.

7. A process according to any one of the preceding claims, wherein the acid buffering salt is selected from the mono-basic phosphates of sodium, potassium or ammonium.

8. Minute capsules each consisting of a seamless wall of ethyl cellulose retaining at least one particle of acetylsalicylic acid coated with a buffering salt selected from the monobasic phosphates of sodium, potassium or ammonium.

9. A process for the encapsulation of minute particles of acetylsalicylic acid according to Claims 1 to 7, substantially as hereinbefore described.

10. Minute capsules prepared by the process according to Claims 1 to 7, substantially as hereinbefore described.

E. T. BEAVIS,
Agent for the Applicants.

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